BODY SIZE MISMATCH BETWEEN DONOR AND RECIPIENT IN CADAVERIC KIDNEY TRANSPLANTATION

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1998

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A Thesis Submitted to the Yale University School of Medicine in Partial Fulfillment of the Requirements for the Degree of Doctor of Medicine

by

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1998

Abstract

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Recently much attention has focused on antigen independent mechanisms as major contributors to late renal allograft loss. Nephron under-dosing at the time of transplantation has been proposed to cause hyperfiltration and ultimately renal graft failure[1]. Kidney size and nephron number have been successfully correlated with body surface area (BSA)[2-3]. Using BSA as a proxy for nephron number, we investigated the relationship between matching donor and recipient BSA and cadaveric renal allograft survival. We studied the United Network of Organ Sharing renal transplant population in this retrospective study using logistic and Cox regression analyses as well as actuarial survival curves. These analyses revealed that a higher probability of graft failure was associated with younger non-white recipients, older non-white donors, increased creatinine at discharge, treatment for rejection before discharge, and a smaller BSA ratio of donor to recipient. Our results demonstrate that while body size matching does affect long-term graft survival, its effect is weaker than the more important determinants of long-term graft survival, like creatinine at discharge, episodes of acute rejection before discharge, recipient race, and recipient and donor age. Therefore, it does not appear that size matching will significantly decrease the incidence of long-term allograft loss in cadaveric renal transplantation.

Acknowledgements

Four years ago I stepped into Dr. Giacomo Basadonna's office as an eager YMS I looking for that perfect thesis project: short and fruitful. Although it became quickly evident that the former would not be true, the latter has certainly surpassed my dreams. I would like to thank Dr. Basadonna for supporting me all these years, through all the stacks of SAS outputs, any time of day or night. Thank you for the incredible opportunity to take my first trip to Europe. I will always cherish that trip to Barcelona, and in many ways, that was the turning point in my medical school career. Thank you also for your continued support despite my choosing internal medicine!

I would also like to thank Luiz Auersvald who so patiently taught me how to cannulate the bile duct in countless mice and supported me through all my frustrations with the computer. And what a blessing it was to go to Spain with someone who could speak the language!

Thank you to Elizabeth Claus who, while she was still an intern in general surgery, tirelessly pored over the bewildering array of SAS outputs and patiently taught a novice statistician.

I would also like to thank my friends who agonized with me as I frantically made poster after poster. Thank you for your support through prayers as well as practical service.

Thank you to my parents who have always supported and encouraged me with such love and wisdom.

Finally, I would like to thank and praise Jesus Christ, my Savior, who truly works miracles everyday of my life. By His grace He brought me to Yale, and by His grace He has blessed me beyond my dreams through my friends, colleagues, teachers, and experiences at Yale. Thank You and may all the glory be to You for all of eternity.

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Introduction

With the advent of immunosuppressive drugs and improved post-transplant care, short-term patient and graft survival following renal transplantation has steadily improved over the past decade. One year graft survival rates range from 75% to over 80%[1]. However, the rate of late graft loss after the first post-transplant year has remained unchanged[1]. Chronic rejection is the leading cause of late graft loss and accounts for 24%-67% of this graft loss[4-6]. Other significant causes include patient death with a functioning transplant and noncompliance[4-6].

Clinically chronic rejection is characterized by a gradual decline in glomerular filtration rate, and is associated with proteinuria and hypertension after the first three or six months post-transplantation[7-8]. Unlike with acute rejection, chronic rejection does not respond to increased amounts of immunosuppressives. Histologically chronic rejection may resemble acute rejection or grafts with no apparent dysfunction with mild to moderate tissue infiltration by T cells and macrophages. In addition, chronic rejection is characterized by vascular, glomerular, and tubulointerstitial lesions[7].

Both immunologic and nonimmunologic factors have been implicated in late renal allograft loss. Evidence supporting immune mediated mechanisms of late graft loss include the greater frequency of chronic rejection in recipients of cadaveric rather than living-related transplants[9], the association of acute rejection with the development of chronic rejection[10,11], and the possible connection between chronic rejection and inadequate immunosuppression secondary to noncompliance or concerns of the nephrotoxic side effects of cyclosporine-A[11]. Several hypotheses have been proposed to explain the immunologic basis for chronic rejection. $CD4^+$ T helper cells coordinate the immune response among the antigen presenting cells, macrophages, cytotoxic T cells, and B cells through the release of cytokines. It is well known that two types of $CD4^+$ T

helper cells exist: TH1 clones which produce IFN-γ and TNF-β leading to macrophage and cytotoxic T cell activity and TH2 clones whose cytokines promote antibody production[12]. One hypothesis proposes that chronic rejection is the result of numerous acute rejection episodes mediated by TH1 activated macrophages and cytotoxic T cells. Another hypothesis argues that immunosuppression of TH1 cells leads to the dominance of TH2 cells, which predominantly cause antibody-mediated graft damage leading to chronic rejection. Whether chronic rejection results from a cellular or humoral mediated mechanism, the target vascular antigen appears to be endothelial cells. Early vascular rejection is correlated with late graft loss; i.e., the five year graft survival rate in this group is 34% compared to 70% to 75% survival in patients never experiencing acute rejection or having only interstitial rejection on biopsy[7].

Recently much attention has focused on potential nonimmunologic factors contributing to late graft loss. These include glomerular hyperfiltration, nephron dosing, renal ischemic injury, systemic hypertension, hyperlipidemia, and drug toxicity. In many animal models of renal injury, the adaptive changes of glomerular hyperfiltration and hypertension have been shown to contribute to the progression of renal damage[13]. Glomerular hyperfiltration and hypertension may lead to glomerulosclerosis and loss of renal function.

Nephron dosing refers to the concept that when the metabolic demands exceed the limit imposed by the nephron number, renal fibrosis is more likely to occur[13]. Loss of renal mass leads to adaptive changes, including an increase in size and function of the remaining nephrons. Animal models have demonstrated that a decrease in renal mass may lead to proteinuria and glomerulosclerosis[14-17]. Clinical evidence exists to support the nephron dosing hypothesis. Long-term graft survival of kidneys from donors that are older (>50 years old), younger (≤6 years old), or female and obese recipients is

decreased[18,19]. Conflicting evidence exists regarding the impact of donor-recipient body size mismatch on long-term graft survival[20-23].

Delayed graft function due to renal ischemic injury occurs in 25% to 50% of cadaveric transplant recipients[13]. Long-term graft survival is decreased in recipients with delayed graft function[24]. Both immunologic as well as nonimmunologic mechanisms may explain the contribution of delayed graft function to late graft loss. Studies have shown that ischemia leads to the upregulation of class-II antigen expression on renal endothelial cells, making the kidney more antigenic[25]. In addition, loss of renal mass from ischemic injury leads to hyperfiltration and renal dysfunction.

Systemic hypertension has been negatively correlated with graft survival[26]. In patients with chronic rejection, the degree of hypertension has been shown to correlate with the severity of histologic change and the rate of decline of renal function. Few studies have addressed the efficacy of the various antihypertensives in reducing the rate of late graft loss. However, calcium-channel blockers are the agents of choice post-transplant because they also reduce cyclosporine-induced nephrotoxicity. Angiotensin-converting-enzyme inhibitors are used with caution because the combination with cyclosporine has been shown to lead to acute renal failure[15].

Pretransplant hyperlipidemia is a risk factor for late graft loss[7]. Oxidatively modified LDL enhances a patient's immune response[13], and LDL is directly toxic to endothelial cells[7]. Although renal damage itself may lead to the lipid abnormalities, studies showing the presence of apolipoproteins in the vessel wall of grafts with chronic rejection and vascular intimal hyperplasia in patients with pretransplant hypercholesterolemia suggest that hyperlipidemia leads to graft atherosclerosis[7,13].

Cyclosporine induces interstitial fibrosis by both causing ischemic damage from chronic vasoconstriction and directly activating interstitial matrix formation[13]. Lower doses of cyclosporine have been shown to cause an initial but not progressive decline in

glomerular filtration rate[13]. However, too low doses of cyclosporine can lead to increased rates of acute and chronic rejection[11].

In this study we investigated the impact of the nonimmunologic factor of nephron dosing on late renal allograft loss. We characterized a nationwide cadaveric renal transplant patient population with respect to body size matching and examined the relationship between donor/ recipient BSA ratio and renal allograft loss.

Statement of Purpose

We intend to answer the question, 'does body size matching affect long-term renal allograft survival?' using a retrospective study to investigate 25,092 patients from the United Network of Organ Sharing (UNOS) Scientific Renal Transplant Registry.

Methods

Data regarding 25,092 patients who underwent cadaveric renal transplantation between October 1, 1987 and December 31, 1993 were obtained from the UNOS Scientific Renal Transplant Registry. Among them, 3039 patients experienced graft loss and the 22,053 patients who maintained good graft function at last follow-up were used as controls. Descriptive statistics were performed by donor/ recipient status for cases and controls using means and percentages. Differences in demographic and clinical variables between cases and controls by donor/ recipient status were assessed using t-tests and chi-square tests for continuous and binary variables, respectively. The independent variable of interest, body surface area ratio (BSR), was defined as BSA donor/ BSA recipient where BSA was calculated according to the following formula (Costeff's rule): BSA (m^2) = (4*weight (kg) + 7)/ (90+weight)[27]. Additional independent variables included age, gender, and race of recipient and donor as well as creatinine of recipient at discharge, number of transplants, and treatment for rejection before discharge.

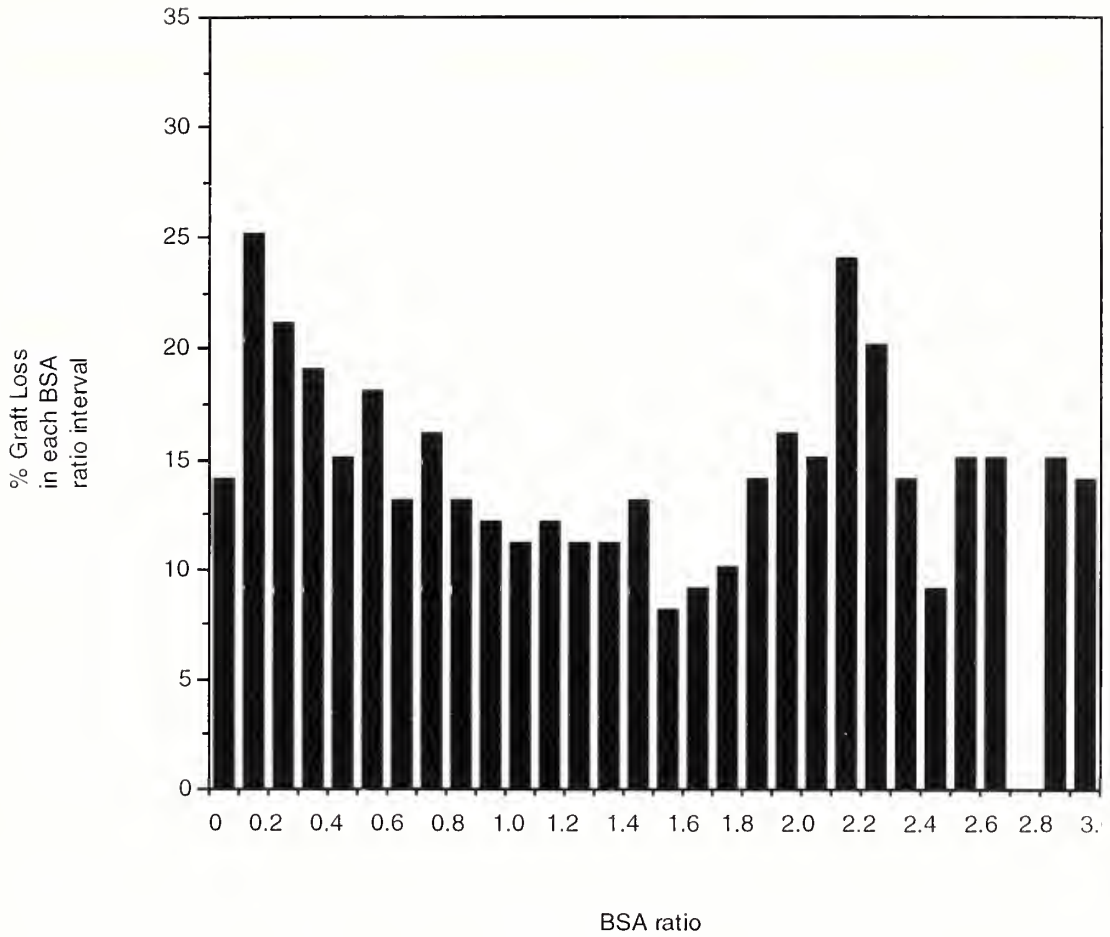
The outcome variable, renal graft loss, was analyzed both as a binary variable (graft loss/ no graft loss) and as a continuous variable (time to graft loss). Logistic regression was used to measure the effect of BSR on the probability of graft loss while a Cox proportional hazards model was used to measure the impact of BSR on the time to graft loss. The logistic and Cox regression models provided unadjusted odds ratios and relative risks, respectively, with 95% confidence. Significant variables associated with allograft loss on univariate analysis were incorporated into a multivariate model to obtain adjusted odds ratios and relative risks. Multivariate analyses were conducted using the stepwise selection procedure with entry and exit criteria set at p=0.05.

Initially the effect of BSR on graft loss and time to graft loss was examined with BSR as a continuous variable. To obtain a more clinically meaningful odds ratio, BSR was also redefined by pairs of binary dummy variables. These variables allowed comparison of graft loss rates among four categories of BSR: 0-0.80, 0.81-1.50, 1.51-1.80, and >1.80 with 0-0.80 as the baseline category. These cut points were selected based upon the distribution of graft loss rates by BSR grouping (Figure 1).

Kaplan-Meier curves and log-rank tests were used to compare the renal graft survival curves of patients in the four different BSR groups. Renal graft survival was also analyzed by subgrouping the recipients by gender and race.

Data are expressed as means ± SE. All analyses were performed using PC-SAS version 6.05.

Figure 1. Proportion of Graft Loss in BSA ratio Intervals



Results

Recipient characteristics are shown in Table 1. Control and case recipients were well matched for gender only while the donors for the controls and cases were significantly different regarding each of the demographic variables. Mean BSA ratio for all recipients was 1.00 ± 0.002. The mean difference in BSA between the paired donor and recipient of the controls was 0.036 ± 0.003. This was significantly different from that between the paired donor and recipient of the cases (0.098 ± 0.008). Therefore, the controls were better size-matched than the cases. Median number of days of follow-up was 687 days by which time 78.6% (2389) of the 3039 graft losses had occurred. By the first 400 days post-transplantation, 47% of the graft losses had occurred. At five years the number of recipients without graft failure and remaining in follow-up was 105.

Univariate analyses of the variables revealed that recipient age and race, donor age, gender, and race, creatinine at discharge, number of transplants, treatment for rejection before discharge, and BSA ratio all had a significant effect on graft loss (Tables 2, 3). Recipients with a BSA ratio ≤0.8 had a 1.479 greater risk of graft loss compared to those with a BSA ratio >0.8. Similar results were obtained with the multivariate logistic and Cox analyses (Tables 2, 3). A higher probability of renal graft loss was associated with the younger, non-white recipient treated for rejection before discharge with a high discharge creatinine and a BSA ratio ≤0.8 who receives a renal graft for the second or third time from an older, non-white, female donor. The most important determinants of graft failure were creatinine at discharge, treatment for rejection before discharge, and recipient age and race. Although a relatively weak risk factor for graft loss, BSA ratio was more important than donor age and race (donor race and transplant number in the Cox regression model). Only donor gender (and number of transplants in the logistic model) was not a significant risk factor for graft loss in the multivariate analyses.

Table 1. Donor and Recipient Characteristics

	Control		Case	
	recipient	donor	recipient	donor
mean age	42.2 ± 0.09*	30.7 ± 0.11*	39.2 ± 0.25*	32.6 ± 0.32*
male / female	61 / 39	64 / 36*	60 / 40	60 / 40*
white / non-white	75 / 25*	89 / 11*	63 / 37*	86 / 14*
mean creatinine at discharge	2.27 ± 0.01*		3.31 ± 0.05*	
treated for rejection before discharge (N/Y)	3.0*		1.8*	
1º / retransplant	19.0*		15.7*	
mean D/R BSA ratio	1.01±0.002*		0.98±0.007*	

* p value <0.05

Table 2. Logistic Regression: Graft Loss (n=25,092)

	Univariate		Multivariate	
Independent variable	p value*	Odds ratio (95% Confidence Interval)	p value**	Odds ratio (95% Confidence Interval)
creatinine at discharge	0.0001	1.180 (1.163, 1.198)	0.0001	1.148 (1.130, 1.165)
treated for rejection before discharge (Y/N)	0.0001	1.688 (1.558, 1.828)	0.0001	1.571 (1.448, 1.705)
recipient race (non-white vs. white)	0.0001	1.722 (1.590, 1.864)	0.0001	1.519 (1.397, 1.651)
recipient age	0.0001	0.984 (0.981, 0.987)	0.0001	0.983 (0.980, 0.986)
D/R BSA ratio	0.0001	1.451 (1.258, 1.675)	0.0001	1.541 (1.342, 1.715)
D/R BSA ratio group (≤0.8 vs. >0.8)	0.0001	1.479 (1.344, 1.631)	0.0001	1.567 (1.404, 1.751)
donor age	0.0001	1.007 (1.005, 1.010)	0.0001	1.009 (1.006, 1.012)
donor race (non-white vs. white)	0.0001	1.365 (1.223, 1.523)	0.0002	1.237 (1.102, 1.388)
number of transplants (retransplant vs. 1°)	0.0027	1.262 (1.084, 1.469)	-	-
donor gender (female vs. male)	0.0001	1.208 (1.118, 1.306)	0.0481	1.088 (1.001, 1.182)

* p value< 0.05
** p value< 0.006

Table 3. Cox Regression: Graft Loss (n= 25,092)

	Univariate		Multivariate	
Independent variable	p value*	Risk ratio (95% Confidence Interval)	p value**	Risk ratio (95% Confidence Interval)
creatinine at discharge	0.0001	1.070 (1.065, 1.075)	0.0001	1.062 (1.056, 1.068)
recipient race (non-white vs. white)	0.0001	1.657 (1.540, 1.783)	0.0001	1.519 (1.416, 1.646)
treated for rejection before discharge (Y/N)	0.0001	1.581 (1.468, 1.703)	0.0001	1.535 (1.425, 1.653)
recipient age	0.0001	0.987 (0.985, 0.990)	0.0001	0.987 (0.984, 0.989)
donor age	0.0001	1.009 (1.007, 1.011)	0.0001	1.012 (1.010, 1.015)
D/R BSA ratio	0.0001	1.468 (1.281, 1.683)	0.0001	1.676 (1.534, 1.841)
D/R BSA ratio group (≤0.8 vs. >0.8)	0.0001	1.449 (1.325, 1.584)	0.0001	1.585 (1.436, 1.750)
donor race (non-white vs. white)	0.0001	1.396 (1.262, 1.545)	0.0001	1.313 (1.183, 1.457)
number of transplants (retransplant vs. 1°)	0.0001	1.321 (1.148, 1.520)	0.0010	1.270 (1.102, 1.463)
donor gender (female vs. male)	0.0001	1.215 (1.130, 1.306)	0.0393	1.084 (1.004, 1.171)

* p value< 0.05
** p value< 0.006

Recipients in the BSA ratio group >0.8 had a significantly higher 5 year actuarial graft survival rate than recipients with a BSA ratio ≤0.8 (controls: 78%, cases: 74%) (Figure 2). The difference in survival rate between the two patient groups remained around 4% throughout the entire 5 year period studied. Similar results were obtained when 5 year actuarial graft survival rates were compared for patients with extreme BSA ratios (group 1: ≤0.5, group 2: 0.95-1.05, group 3: ≥1.5). The 5 year graft survival rate of group 1 was 4% lower than the other 2 groups ($p<0.05$). Analyses of recipients first subdivided according to race or gender and then by BSA ratio group revealed the same results. There was also a significant effect on graft survival by race alone.

The recipients were reanalyzed after removing those patients who had lost their renal grafts within the first year post-transplantation. Recipients who lost their grafts were younger with more non-whites, a higher mean creatinine at discharge, and more treatment for rejection before discharge than the control recipients ($p<0.05$). The gender distribution and mean BSA ratio for the two recipient groups were not significantly different. The donors for the recipients who lost the grafts were older with more non-whites ($p<0.05$). Multivariate analyses revealed similar results as with all the patients (Tables 4, 5). However, the Kaplan-Meier actuarial graft survival curves did not show a significant difference in survival rates between recipients with a small (≤0.8) versus a large (>0.8) BSA ratio.

There were 1814 transplantations from pediatric donors ≤10 years of age. Of these, 1616 recipients had a BSA ratio ≤0.8 while the other 198 had a BSA ratio >0.8. There was no difference in the 5 year graft survival rates for the two BSA ratio groups. However, these recipients of pediatric kidneys had a 2% lower graft survival rate at five years than recipients with adult donors ($p<0.05$).

Figure 2. Survival of Kidney Grafts according to BSA ratio

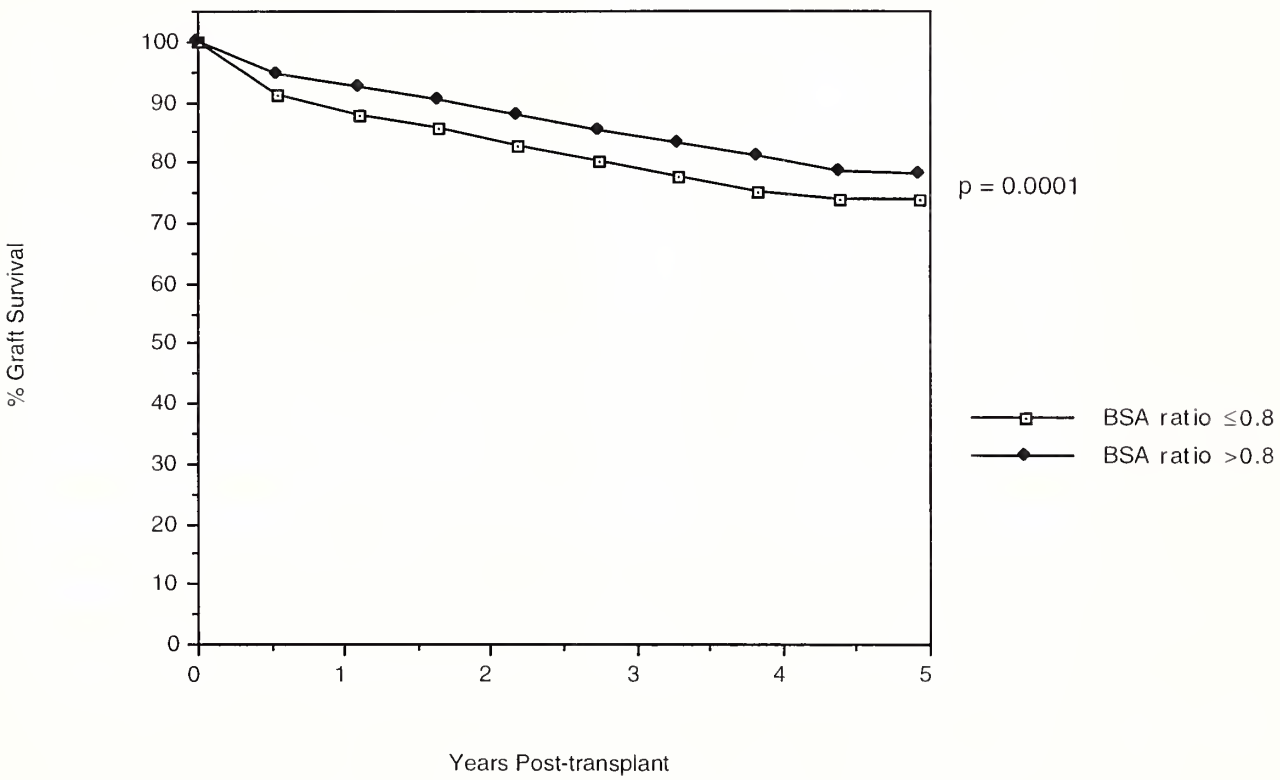


Table 4. Logistic Regression: Graft Loss ≥1year post-transplantation (n=23237)

	Multivariate	
Independent variable	p value*	Odds ratio (95% Confidence Interval)
recipient race (non-white vs. white)	0.0001	2.349 (2.085, 2.647)
recipient age	0.0001	0.973 (0.969, 0.978)
donor age	0.0001	1.009 (1.005, 1.013)
treated for rejection before discharge (Y/N)	0.0001	1.296 (1.140, 1.473)
D/R BSA ratio group (≤0.8 vs. >0.8)	0.0019	1.311 (1.105, 1.556)
creatinine at discharge	0.0052	1.030 (1.009, 1.051)

* $p<0.006$

Table 5. Cox regression: Graft Loss ≥1 year post-transplantation (n=23237)

	Multivariate	
Independent variable	p value*	Risk ratio (95% Confidence Interval)
recipient race (non-white vs. white)	0.0001	2.341 (2.084, 2.630)
recipient age	0.0001	0.977 (0.973, 0.981)
donor age	0.0001	1.015 (1.011, 1.019)
creatinine at discharge	0.0001	1.039 (0.883, 1.057)
D/R BSA ratio group (≤0.8 vs. >0.8)	0.0001	1.374 (1.167, 1.617)
treated for rejection before discharge (Y/N)	0.0073	1.183 (1.046, 1.338)
donor race (non-white vs. white)	0.0231	1.217 (1.027, 1.442)
number of transplants (retransplant vs. 1°)	0.0370	1.285 (1.015, 1.625)

* p value< 0.006

Discussion

Long-term renal allograft survival remains unchanged despite tremendous advances in immunosuppression and post-transplant care. Recently much attention has been focused on antigen independent mechanisms as major contributors to late renal allograft loss. Rat models, including Shimamura and Morrison's five-sixths nephrectomy model[14], Hostetter and colleagues' eleven-twelths model[28], and Brenner and associates' five-sixths model[15], have all demonstrated the deleterious effect of nephron dosing on long-term renal graft survival. Reductions in nephron mass to one-sixth accelerated the development of proteinuria and glomerulosclerosis regardless of the immunogenicity of the transplanted organ[15]. Leaving a native kidney in the transplanted rats protected them from these changes[16]. Furthermore, expression of cell surface molecules, cytokine production, and infiltration of macrophages in renal tissue was modulated by nephron mass[17].

Several natural and man-made experiments in human beings exist that assess the nephron dosing hypothesis. These models include unilateral renal agenesis, unilateral nephrectomy for renal disease, and donor nephrectomy. Unilateral renal agenesis is associated with an increased incidence of proteinuria and focal segmental glomerulosclerosis. Long-term follow-up of patients with unilateral nephrectomy secondary to renal disease or donor status failed to demonstrate these adverse outcomes. However, proteinuria and focal segmental glomerulosclerosis occurred in patients with a single kidney who further underwent between 25% and 75% nephrectomy of this solitary kidney for renal carcinoma[29].

Clinical evidence exists to suggest a link between nephron dosing and long-term graft outcome. Diminished graft survival is associated with donors who are aged 4 to 6, older (>50), female, black, or cadaveric, obese recipients (>100kg), and kidneys that

experienced rejection episodes[18,19,30]. The ideal experiment to demonstrate the impact of nephron dosing on long-term graft survival in human beings would replicate the animal studies by comparing single versus double kidney transplants. However, this is hardly feasible given the grave disparity between the supply and demand for kidneys. No prospective data exist. Therefore, we were limited to a retrospective study of single kidney recipients.

Several retrospective studies have examined the impact of donor/ recipient size matching on long-term graft survival. Kupin and colleagues found lower donor/ recipient BSA ratios (0.88±0.1) in recipients with transplant glomerulopathy than in those with normal graft function (1.0±0.2). However, the former recipients had other reasons to develop graft failure, including 84% being African American who were poorly HLA matched with multiple episodes of acute rejection[20]. The ratio of donor kidney weight to recipient body weight did not impact graft survival in over 300 patients studied by Roth and co-workers[21]. Miles and associates studied over 150 patients using the ratio of renal volume to recipient BSA and found no effect on graft survival[22]. Similarly, the variable of interest, the ratio of donor/ recipient BSA, for Gaston and colleagues did not affect graft survival and renal function as measured by serum creatinine levels[23].

Our study is the largest to date and may explain the different results obtained from Roth *et al.*, Miles *et al.*, and Gaston *et al.* The studies to date examining the effect of donor/ recipient size matching suggest that whatever impact nephron dosing has on long-term renal allograft survival is overshadowed by other clinical parameters. Our study confirms these findings. We have demonstrated that the donor/ recipient BSA ratio of cadaveric renal transplants in the United States does have a statistically significant impact on long-term allograft loss. However, its effect is weak compared to the most important determinants of long-term graft survival like creatinine at discharge, episodes of acute rejection, and recipient race. These results were duplicated when we analyzed only the

patients with a graft surviving for at least one year post-transplantation. In comparing the four categories of BSA ratio, recipients with a BSA at least 20% larger than their donors fared worse than the recipients with a smaller BSA in both the multivariate regression and survival analyses. The former recipients experienced a 4% lower survival rate which remained constant throughout the 5 year follow-up. This absolute value, while statistically significant, was not impressive. In the nephron dosing hypothesis, one may expect the survival curves to diverge over the years as the allograft loses more nephrons. This was not seen in our analyses using the four original as well as the three extreme BSA ratio categories.

In examining the patient population, the majority of recipients were already well size matched. Although the difference in mean BSA ratios between the controls and cases was statistically significant, the absolute values revealed a negligible difference (controls: 1.01, cases: 0.98). Similarly, while the mean difference in BSA between the pairs of donors and recipients for the controls versus the cases was significantly different, the actual numbers were not impressive (controls: 0.036, cases: 0.098). However, the trend of these values with the recipients experiencing graft loss being slightly larger than their donors and more poorly size matched with their donors than the control recipients supports the idea that recipients with a smaller nephron dose are more likely to develop late graft failure.

In this retrospective study using donor/ recipient BSA ratio as a surrogate for nephron dosing, we demonstrate that while body size matching does affect cadaveric renal allograft survival up to 5 years post-transplantation, its effect is overshadowed by other clinical factors. Therefore, it does not appear that prospective size matching will significantly decrease the incidence of late allograft loss in cadaveric renal transplant recipients.

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